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# Lewis acid promoted fluorine-alkoxy group exchange reactions for the synthesis of 5-alkoxy-4,4-difluoroisoxazoline systems

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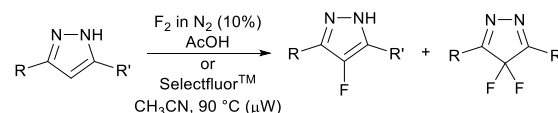
Fluorine-alkoxy group exchange reactions of fluorinated isoxazoline derivatives promoted by Lewis acids to give various 5-alkoxylated 4,4-difluoroisoxazolines via S<sub>N</sub>1 type processes in good to excellent yields are reported. Sterically demanding phenol substrates such as 2,6-diphenylphenol gave novel aryl substituted products via electrophilic aromatic substitution.

## Introduction

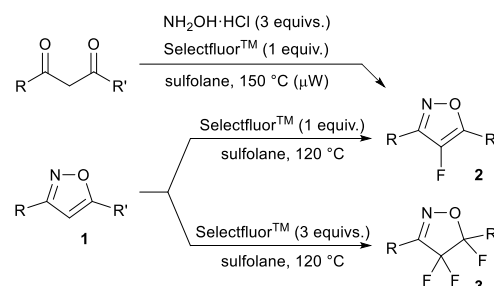
Fluorinated heterocyclic systems can have unique biological activity and, therefore, many fluorinated pharmaceutical and agrochemical substances which contain fluoro-aromatic or heterocyclic moieties have been reported.<sup>1</sup> For the purpose of synthesizing some fluorinated heterocyclic systems, electrophilic fluorinating agents of the N-F class such as *N*-fluoropyridinium salts (F-Py-X), Selectfluor<sup>TM</sup>, and NFSI are commonly used due to the relative ease of handling these shelf-stable, crystalline solids and their wide commercial availability.<sup>2</sup> Further examples of recently reported methodology for introducing fluorine atoms into heterocyclic scaffolds include selective fluorination at the 2-position of pyridines or pyrimidines by using AgF<sub>2</sub> reported by Hartwig,<sup>3</sup> Ritter and his group have developed a new fluorinating reagent 'PhenoFluor' for the transformation of a wide variety of hydroxylated substrates to corresponding fluorinated systems and Yamaguchi and his co-workers reported a Rh-catalyzed heteroaryl aryl ether exchange reaction which was applied to various heterocyclic substrates to give the corresponding fluorinated products in good yields.<sup>4,5</sup>

While synthetic routes to many fluorinated 6-membered heteroaromatic ring systems such as fluoro-pyridine<sup>6</sup>, -pyrimidine<sup>7</sup> and -pyrazine<sup>8</sup> have been reported, in particular, there remains a surprising lack of general synthetic methodology for the preparation of corresponding fluorinated 5-membered heteroaromatic systems that have two heteroatoms, such as pyrazoles<sup>9</sup>, isoxaols<sup>10</sup> and thiazoles<sup>11</sup>. In this context, we reported selective fluorination of pyrazoles to give 4-fluoropyrazoles or unexpected 4,4-difluoro-1*H*-pyrazoles depending on the conditions (Scheme 1).<sup>12</sup> Furthermore, similar reaction conditions allowed us to fluorinate isoxazoles (**1**) to give 4-fluorinated isoxazoles (**2**) or 4,4,5-trifluorinated isoxazolines (**3**), respectively (Scheme 2).<sup>13</sup> During the process of 4,4,5-

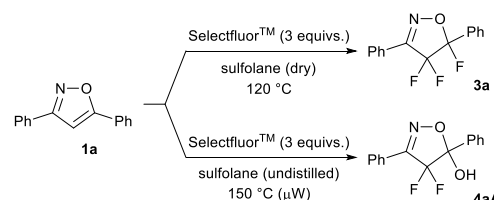
trifluorinated isoxazoline synthesis, we found that it was very important to use dry solvents to give the desired product because generation of 4,4-difluoro-5-hydroxylated derivatives (**4aA**) occurred when using undistilled commercially available 'wet' sulfolane (Scheme 3).



Scheme 1. Direct or selective fluorination of pyrazoles.<sup>12</sup>



Scheme 2. Selective fluorination of isoxazoles.<sup>13</sup>



Scheme 3. 4,4,5-Trifluoroisoxazolines and 4,4-difluoro-5-hydroxyisoxazolines.<sup>13</sup>

Following this outcome, we set out to explore the fluorine-alkoxy group exchange reaction as part of a research program aimed at synthesizing a wide range of functional fluorinated 5-membered heterocyclic systems and, in this paper, we report the synthesis of novel 5-alkoxylated 4,4-difluoroisoxazoline derivatives.

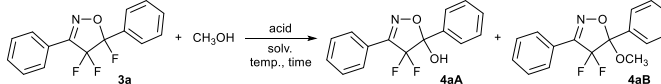
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## Results and Discussion

We postulated that the introduction of a hydroxyl group on isoxazoline substrates (Scheme 3) was caused by the presence of water, so to confirm this 4,4,5-trifluorinated isoxazoline **3a** was treated with HCl or NaOH (entries 1 and 2 of Table 1).

Table 1. 5-Hydroxylation and 5-alkoxylation.



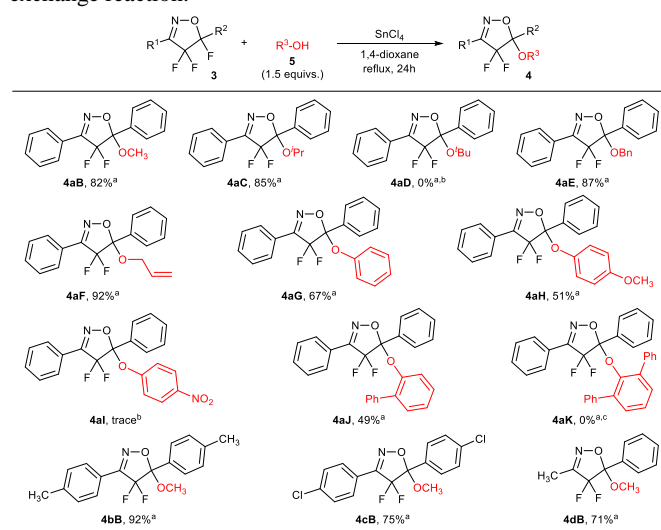
Entry	CH <sub>3</sub> OH	Solv.	Acid (equiv.)	Temp. (°C)	Time (h)	Yield <sup>a</sup>	
						<b>4aA</b>	<b>4aB</b>
1	—	—	HCl (2 mL)	70	24	nd	nd
2	—	—	NaOH (2 mL)	70	24	nd	nd
3	—	methanol (2 mL)	HCl (1 mL)	reflux	42	32	50
4	—	THF (2 mL)	HCl (1 mL)	70	24	nd	nd
5	—	1,4-dioxane (2 mL)	HCl (1 mL)	reflux	24	78	nd
6	—	sulfolane (2 mL)	HCl (1 mL)	80	29	68	nd
7	1 mL	1,4-dioxane (2 mL)	Sc(OTf) <sub>3</sub> (1)	reflux	24	nd	94
8	1 mL	1,4-dioxane (2 mL)	Sc(OTf) <sub>3</sub> (0.1)	reflux	48	(28) <sup>b</sup>	78
9	1 equiv.	1,4-dioxane (3 mL)	Sc(OTf) <sub>3</sub> (1)	reflux	24	(84) <sup>b</sup>	18
10	1 equiv.	1,4-dioxane (3 mL)	BF <sub>3</sub> ·Et <sub>2</sub> O (1)	reflux	24	(26) <sup>b</sup>	62
11	1 equiv.	1,4-dioxane (3 mL)	LiCl (1)	reflux	24	nd	nd
12	1 equiv.	1,4-dioxane (3 mL)	InBr <sub>3</sub> (1)	reflux	24	nd	nd
13	1 equiv.	1,4-dioxane (3 mL)	SnCl <sub>4</sub> (1)	reflux	24	(14) <sup>b</sup>	78
14	1 equiv.	1,4-dioxane (3 mL)	SnCl <sub>2</sub> (1)	reflux	24	(55) <sup>b</sup>	37
15	1.5 equivs.	1,4-dioxane (3 mL)	SnCl <sub>4</sub> (1)	reflux	24	(20) <sup>b</sup>	82

<sup>a</sup>Isolated yield. <sup>b</sup>Approximate yield of **4aA** because of unseparable side products.

However, these reactions did not give the product **4aA** at all because **3a** did not dissolve into water. Therefore, we examined reactions of **3a** in mixtures of water and various co-solvents and, indeed, when a mixture of 1,4-dioxane and water was used, the desired hydroxylated product **4aA** was obtained in high yield (entry 5). Additionally, using methanol as the co-solvent gave 5-methoxylated product **4aB** in 50% yield along with **4aA** (entry 3) indicating that various alcohols could be used for introducing alkoxy groups by similar processes. Therefore, we first examined reaction conditions for 5-methoxylation of **3a** and these results are summarized in Table 1. Based on similar conditions, various Lewis acids were used in the presence of methanol. As shown in entries 7–9, Sc(OTf)<sub>3</sub> was used as the Lewis acid and gave **4aB** in an excellent yield when using excess MeOH. On the other hand, using a catalytic amount of Sc(OTf)<sub>3</sub> or one equivalent of MeOH caused a decrease in yield. As the various examinations, when **3a** was treated with 1.5 equivalents of methanol and 1.0 equiv. of SnCl<sub>4</sub>, a high yield of **4aB** was obtained (entry 15).

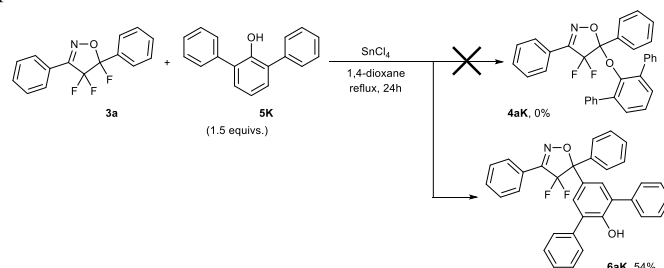
On the basis of the optimized conditions (entry 15, Table 1), various alkoxylation reactions of **3** using a variety of alcohol substrates were investigated and these results are in Table 2.

Table 2. Scope and limitations for fluorine-alkoxy group exchange reaction.



<sup>a</sup>Isolated yield. <sup>b</sup>The main product was 5-hydroxylated product (**4aA**).  
<sup>c</sup>The main product was 5-(*p*-arylated) product (**6aK**).

Reactions of **3** with methanol, *isopropanol*, benzylalcohol and allyl alcohol gave the desired alkoxyated products **4** in good to excellent yields. On the other hand, reaction with *tert*-butanol did not give the alkoxyated product at all and the main product in this case was 5-hydroxylated product **4aA** reflecting the steric hindrance of the nucleophile. Phenol and *p*-methoxyphenol gave the corresponding phenoxylated products in 67% and 51% yield, respectively. However, for the reaction of **3a** with *p*-nitrophenol, while the desired product was identified by <sup>19</sup>F NMR, it was very difficult to separate from unidentified side products and 5-hydroxylated product **4aA** was the only product isolated pure. 2-Phenylphenol gave the desired phenoxylated product in 49% yield whereas 2,6-diphenylphenol gave only 5-(*p*-arylated)product (**6aK**) in 54% yield (Scheme 4). It is interesting that the chemical shift difference of the fluorine atoms is generated between **4** and **6**. In the products **4**, the diastereotopic fluorine resonance at around -30 ppm would be the *cis* form to the aromatic ring, and the other fluorine resonance at around -60 ppm would be the *cis* form to the OR group. In contrast, both fluorine resonances were observed at around -30 ppm in **6aK**.



Scheme 4. Generation of 5-(*p*-arylated) product (**6aK**).

Analogous *p*-toluyl and *p*-chlorophenyl starting materials, **3b** and **3c** respectively, were treated with methanol under the same conditions to give the corresponding products, **4bB** and **4cB**, in 92% and 75%, respectively. In addition, isoxazoline **3d**, bearing methyl and phenyl groups, also gave the alkoxyated product **4dB** in good yield. Therefore, primary and secondary alcohols and phenols are

successful substrates for this 5-alkoxylation reaction which proceeded smoothly to give corresponding products in good to excellent yields, although yields can be influenced by acidity and the bulkiness of the alcohol nucleophiles.

We envisage that the mechanism is a Lewis acid promoted fluorine-alkoxy group exchange reaction via an  $S_N1$  type mechanism (Fig. 1). Starting material **3a** is activated by the Lewis acid to give the carbocation (**Int A**) intermediate, stabilized by the adjacent oxygen atom, which is trapped by alcohol nucleophiles to give **4**. However, 2,6-diphenylphenol is a very sterically hindered oxygen nucleophile and did not give the 5-alkoxylated product **4aK** but 5-(*p*-arylated) product **6aK** via an electrophilic aromatic substitution mechanism.

Proposed reaction mechanism

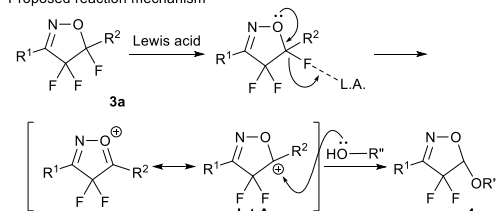
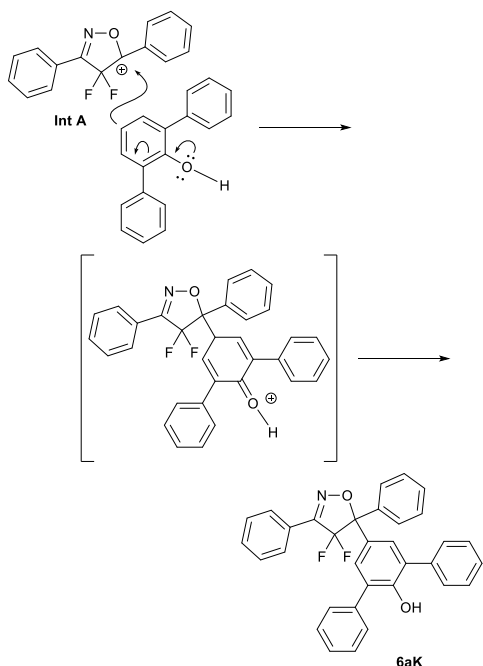
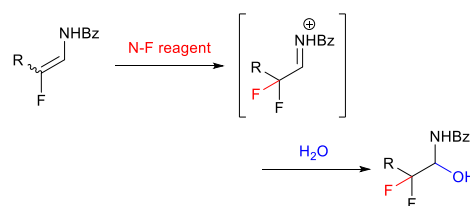
Generation of 5-(*p*-arylated) product **6aK** via electrophilic aromatic substitution mechanism

Figure 1. Proposed reaction mechanism for fluorine-alkoxy group exchange reaction.

Very recently, Prakash and his co-workers reported a direct difluorination-hydroxylation of *iso*-indolinones via oxy-fluorination of enamides.<sup>14</sup> Our system bears a resemblance to this process and we expected the reaction to proceed even if an isoxazole substrate was used in this reaction (Fig. 2). Indeed, the monofluorinated isoxazole (**2a**) was treated with Selectfluor<sup>TM</sup> in the presence of MeOH to give the corresponding difluorinated methoxylated isoxazoline (**4aB**) in 68% (Scheme 5). Furthermore, this alkoxy-fluorination could also be applied to non-fluorinated isoxazole (**1a**) to give same product (**4aB**) in 41%.

Oxy-fluorination of enamides.



Oxy- or alkoxy-fluorination of isoxazoles.

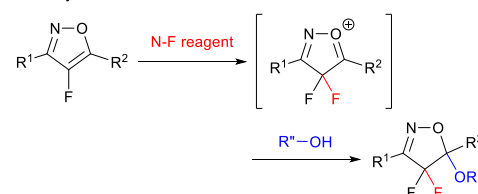
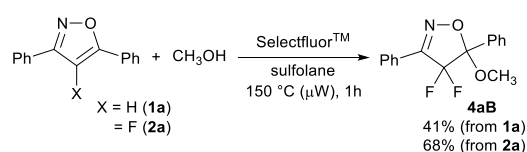


Figure 2. Oxy- or alkoxy-fluorination of isoxazoles.



Scheme 5. Alkoxy-fluorination of isoxazoles.

## Conclusions

In conclusion, Lewis acid promoted fluorine-alkoxy group exchange reactions via  $S_N1$  type processes give 5-alkoxy-4,4-difluoroisoxazoline derivatives. Using primary and secondary alcohols and phenols gave the desired products **4** in good yields, although the acidity and steric demand of **5** affected the yields. A bulky phenol substrate gave the corresponding electrophilic aromatic substitution product **6**. Furthermore, we could achieve the alkoxy-fluorination from isoxazoles to give **4**, directly. Isoxazolines are important scaffolds for bioactive compounds such as medicines and agrochemicals and the synthesis of unique products such as difluorinated 5-alkoxyisoxazolines expands the chemistry of these important structural units.

## Experimental

### General Information.

<sup>1</sup>H NMR, <sup>13</sup>C NMR and <sup>19</sup>F NMR spectra were recorded on JEOL JNM-ECZ400 spectrometers. Chemical shifts of <sup>1</sup>H NMR and <sup>13</sup>C NMR are reported in ppm from tetramethylsilane (TMS: 0 ppm) as an internal standard. Chemical shifts of <sup>19</sup>F NMR are reported in ppm from benzotrifluoride (BTF: 0 ppm) as an internal standard. All data are reported as follows: chemical shifts, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz). Mass spectra were obtained on JEOL JMS-700T spectrometers. IR spectra were recorded on JASCO FT/IR-410 spectrophotometer. Melting points were measured on Yanagimoto micro melting point apparatus MP-

S3. Analytical gas-liquid chromatography (GLC) was carried out on Hitachi G-3500 gas chromatograph (column; TO-5 0.25 mm x 15 m, carrier; He at 2.2 mL/min). Peak areas were calculated on Hitachi D-2500 Chromato-integrator. Microwave reactions were performed in microwave tubes with clip lids using Biotage Initiator+ microwave reactor.

### Materials.

Sulfolane and 1,4-dioxane were distilled before use. All other commercially available reagents were used without further purification. All experiments were carried out under argon atmosphere unless otherwise noted. Syntheses of 4,4,5-trifluoroisoxazolines derivatives (**3**) were reported earlier.<sup>13</sup>

### Synthesis of 4,4-difluoro-3,5-diphenyl-4,5-dihydroisoxazol-5-ol (**4aA**).

4,4,5-Trifluoro-3,5-diphenyl-4,5-dihydroisoxazole (**3a**; 0.4 mmol) was dissolved in HCl–1,4-dioxane solution (3 mL, HCl : 1,4-dioxane = 1:2), and the mixture was heated at reflux for 24 h. The resulting mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with sat. aq. NaCl and dried (MgSO<sub>4</sub>). The solvent was evaporated and the residue was purified by column chromatography (AcOEt : hexane = 1:9) to give **4aA** (86 mg, 78%).

### General procedure for Lewis acid promoted fluorine-alkoxy group exchange reaction.

To a solution of 4,4,5-trifluoroisoxazoline (**3**; 0.4 mmol) and alcohol (**5**, 0.6 mmol) in 1,4-dioxane (3 mL) was added 1.0 M SnCl<sub>4</sub> in heptane (0.4 mL, 0.4 mmol) at ambient temperature and the mixture was refluxed for 24 h. The resulting mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with sat. aq. NaCl and dried (MgSO<sub>4</sub>). The solvent was evaporated and the residue was purified by column chromatography on silica gel to give 5-alkoxy-4,4-difluoroisoxazoline (**4**).

### General procedure for alkoxy-fluorination of isoxazoles.

Isoxazole (**1** or **2**; 1 mmol), MeOH (1.5 mmol) and Selectfluor™ (3 mmol when using **1**, or 2 mmol when using **2**) were added to a microwave vial and suspended in sulfolane (4 mL). The vial was sealed and heated by microwave irradiation for 1h at 150 °C. The resulting mixture was quenched with NaHCO<sub>3</sub> and, extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue was purified by column chromatography to give **4aB**.

### Spectroscopic Data.

#### 4,4-Difluoro-3,5-diphenyl-4,5-dihydroisoxazol-5-ol (**4aA**)

Colorless solid; M.p. 109.0–111.0 °C (recrystallized from hexane–AcOEt); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.96 (1H, s), 7.41–7.53 (6H, m), 7.63–7.66 (2H, m), 7.83–7.85 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 103.0 (dd, *J* = 33.1, 19.4 Hz), 124.6 (dd, *J* = 267.8, 255.2 Hz), 124.9 (m), 126.8 (d, *J* = 1.5 Hz), 127.1 (d, *J* = 1.5 Hz), 128.5, 129.1, 130.3, 131.6, 132.7 (d, *J* = 1.4 Hz), 153.7 (dd, *J* = 25.9, 24.9 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ: -37.54 (1F, d, *J* = 266.3 Hz), -57.23 (1F, d, *J* = 266.3 Hz); MS *m/z*: 275 (M<sup>+</sup>); HRMS Calcd for

C<sub>15</sub>H<sub>11</sub>F<sub>2</sub>NO<sub>2</sub>: 275.076 (M<sup>+</sup>), Found: 275.076; IR (KBr) cm<sup>-1</sup>: 2982, 1450, 1365, 1242, 1127, 1098.

#### 4,4-Difluoro-5-methoxy-3,5-diphenyl-4,5-dihydroisoxazole (**4aB**)

Pale yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.35 (3H, s), 7.44–7.52 (6H, m), 7.63–7.65 (2H, m), 7.85–7.88 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 51.71, 105.3 (dd, *J* = 33.2, 17.5 Hz), 125.0 (m), 125.1 (dd, *J* = 271.6, 252.7 Hz), 126.9 (m), 127.7 (m), 128.7, 129.0, 130.2, 131.5, 154.9 (dd, *J* = 26.1, 24.2 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ: -34.8 (1F, d, *J* = 265.6 Hz), -62.61 (1F, d, *J* = 265.6 Hz); MS *m/z*: 289 (M<sup>+</sup>); HRMS Calcd for C<sub>16</sub>H<sub>13</sub>F<sub>2</sub>NO<sub>2</sub>: 289.091 (M<sup>+</sup>), Found: 289.092; IR (neat) cm<sup>-1</sup>: 3064, 1247, 1130, 1098.

#### 4,4-Difluoro-5-isopropoxy-3,5-diphenyl-4,5-dihydroisoxazole (**4aC**)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.10 (3H, d, *J* = 6.2 Hz), 1.25 (3H, d, *J* = 6.2 Hz), 3.99 (1H, sep, *J* = 6.2 Hz), 7.45–7.53 (6H, m), 7.66–7.68 (2H, m), 7.86–7.87 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 23.66, 23.83, 69.19, 105.6 (dd, *J* = 32.1, 17.3 Hz), 125.1 (dd, *J* = 271.5, 252.7 Hz), 125.3 (m), 126.9 (m), 127.7 (m), 128.4, 129.0, 130.0, 131.4, 131.9 (m), 154.9 (dd, *J* = 26.1, 24.2 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ: -35.4 (1F, d, *J* = 263.8 Hz), -62.3 (1F, d, *J* = 263.8 Hz); MS *m/z*: 317 (M<sup>+</sup>); HRMS Calcd for C<sub>18</sub>H<sub>17</sub>F<sub>2</sub>NO<sub>2</sub>: 317.123 (M<sup>+</sup>), Found: 317.123; IR (neat) cm<sup>-1</sup>: 3063, 2977, 1247, 1129, 1091.

#### 5-(Benzyloxy)-4,4-difluoro-3,5-diphenyl-4,5-dihydroisoxazole (**4aE**)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 4.47 (1H, m), 4.75 (1H, m), 7.24–7.53 (11H, m), 7.69–7.74 (2H, m), 7.86–7.88 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 66.31, 105.2 (dd, *J* = 33.4, 17.6 Hz), 125.0, 125.1 (dd, *J* = 272.2, 251.9 Hz), 126.9, 127.6, 127.7, 127.8, 128.4, 128.7, 129.0, 130.3, 130.6, 131.6, 136.9, 155.0 (dd, *J* = 25.4, 24.8 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ: -34.7 (1F, d, *J* = 265.1 Hz), -62.1 (1F, d, *J* = 265.1 Hz); MS *m/z*: 365 (M<sup>+</sup>); HRMS Calcd for C<sub>22</sub>H<sub>17</sub>F<sub>2</sub>NO<sub>2</sub>: 365.123 (M<sup>+</sup>), Found: 365.123; IR (neat) cm<sup>-1</sup>: 3063, 2977, 1247, 1129, 1091.

#### 5-(Allyloxy)-4,4-difluoro-3,5-diphenyl-4,5-dihydroisoxazole (**4aF**)

Colorless oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.96 (1H, m), 4.20 (1H, m), 5.16 (1H, m), 5.28 (1H, m), 5.89 (1H, m), 7.45–7.53 (6H, m), 7.64–7.67 (2H, m), 7.86–7.88 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 65.53, 105.2 (dd, *J* = 33.3, 17.7 Hz), 117.2, 125.1 (dd, *J* = 272.0, 252.8 Hz), 125.0 (m), 126.9 (m), 127.6 (m), 128.7, 129.0, 130.2, 130.6 (m), 131.5, 133.4, 154.8 (dd, *J* = 26.0, 24.2 Hz); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ: -34.8 (1F, d, *J* = 265.1 Hz), -62.3 (1F, d, *J* = 265.1 Hz); MS *m/z*: 315 (M<sup>+</sup>); HRMS Calcd for C<sub>18</sub>H<sub>15</sub>F<sub>2</sub>NO<sub>2</sub>: 315.107 (M<sup>+</sup>), Found: 315.107; IR (neat) cm<sup>-1</sup>: 3065, 1247, 1130, 1091.

#### 4,4-Difluoro-5-phenoxy-3,5-diphenyl-4,5-dihydroisoxazole (**4aG**)

Pale yellow sticky oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 6.93–7.01 (3H, m), 7.12–7.16 (2H, m), 7.39–7.43 (3H, m), 7.45–7.54 (3H, m), 7.64–7.67 (2H, m), 7.88–7.90 (2H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 105.1 (dd, *J* = 34.1, 17.4 Hz), 120.2, 123.3, 124.7 (m), 125.5 (dd,

$J = 274.2, 253.3$  Hz), 127.0 (m), 127.7, 128.6, 129.1, 129.1, 130.2, 130.4, 131.8, 153.0, 154.9 (dd,  $J = 25.8, 24.3$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -35.1 (1F, d,  $J = 263.4$  Hz), -61.1 (1F, d,  $J = 263.4$  Hz); MS  $m/z$ : 351 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{21}\text{H}_{15}\text{F}_2\text{NO}_2$ : 351.107 ( $\text{M}^+$ ), Found: 351.106; IR (neat)  $\text{cm}^{-1}$ : 3064, 3042, 1591, 1494, 1450, 1247, 1214, 1132, 1061.

#### 4,4-Difluoro-5-(4-methoxyphenoxy)-3,5-diphenyl-4,5-dihydroisoxazole (4aH)

Colorless sticky oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.68 (3H, s), 6.64–6.69 (2H, m), 6.89–6.93 (2H, m), 7.40–7.43 (3H, m), 7.46–7.55 (3H, m), 7.64–7.67 (2H, m), 7.88–7.91 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 55.41, 105.2 (dd,  $J = 33.8, 17.5$  Hz), 114.1, 121.9, 124.8 (m), 125.5 (dd,  $J = 273.8, 253.3$  Hz), 127.0 (m), 127.8 (m), 128.5, 129.1, 130.2, 130.5 (m), 131.7, 146.5, 155.1 (dd,  $J = 26.0, 24.1$  Hz), 155.7;  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -35.0 (1F, d,  $J = 263.8$  Hz), -61.3 (1F, d,  $J = 263.8$  Hz); MS  $m/z$ : 381 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{22}\text{H}_{17}\text{F}_2\text{NO}_3$ : 381.118 ( $\text{M}^+$ ), Found: 381.117; IR (neat)  $\text{cm}^{-1}$ : 3063, 2953, 1247, 1206, 1130, 1063.

#### 5-([1,1'-Biphenyl]-2-yloxy)-4,4-difluoro-3,5-diphenyl-4,5-dihydroisoxazole (4aJ)

Colorless sticky oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.02–7.12 (3H, m), 7.19–7.53 (14H, m), 7.76–7.78 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 105.3 (dd,  $J = 34.2, 17.5$  Hz), 120.4, 123.8, 124.6 (m), 125.5 (dd,  $J = 275.1, 253.4$  Hz), 126.9, 127.0 (m), 127.6, 127.8, 127.9, 128.5, 129.0, 129.8, 130.1, 130.5, 130.9, 131.6, 134.2, 138.0, 149.8, 154.8 (dd,  $J = 25.7, 24.6$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -34.8 (1F, d,  $J = 262.5$  Hz), -59.7 (1F, d,  $J = 262.5$  Hz); MS  $m/z$ : 427 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{27}\text{H}_{19}\text{F}_2\text{NO}_2$ : 427.138 ( $\text{M}^+$ ), Found: 427.139; IR (neat)  $\text{cm}^{-1}$ : 3063, 1600, 1502, 1479, 1247, 1207, 1061.

#### 4,4-Difluoro-5-methoxy-3,5-di-*p*-tolyl-4,5-dihydroisoxazole (4bB)

Colorless solid; M.p. 86.0–86.5 °C (recrystallized from MeOH);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.40 (3H, s), 2.41 (3H, s), 3.33 (3H, s), 7.26–7.30 (4H, m), 7.50–7.53 (2H, m), 7.74–7.76 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 21.36, 21.62, 51.58, 105.2 (dd,  $J = 33.2, 17.7$  Hz), 122.2 (m), 125.1 (dd,  $J = 271.3, 252.4$  Hz), 126.8 (m), 127.2 (m), 127.6 (m), 129.4, 129.7, 140.2, 142.0, 154.8 (dd,  $J = 26.1, 24.2$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -34.9 (1F, d,  $J = 265.1$  Hz), -62.8 (1F, d,  $J = 265.1$  Hz); MS  $m/z$ : 317 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{18}\text{H}_{17}\text{F}_2\text{NO}_2$ : 317.123 ( $\text{M}^+$ ), Found: 317.123; IR (KBr)  $\text{cm}^{-1}$ : 3017, 2976, 2942, 1249, 1127, 1092.

#### 3,5-Bis(4-chlorophenyl)-4,4-difluoro-5-methoxy-4,5-dihydroisoxazole (4bC)

Colorless solid; M.p. 95.5–96.5 °C (recrystallized from MeOH);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.34 (3H, s), 7.44–7.49 (4H, m), 7.54–7.58 (2H, m), 7.78–7.80 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 51.80, 105.0 (dd,  $J = 33.1, 17.6$  Hz), 123.2 (m), 124.8 (dd,  $J = 271.9, 252.9$  Hz), 128.1 (m), 128.5 (m), 129.1, 129.1 (m), 129.5, 136.6, 138.0, 154.1 (dd,  $J = 26.1, 24.2$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -34.9 (1F, d,  $J = 265.5$  Hz), -62.6 (1F, d,  $J = 265.5$  Hz); MS  $m/z$ : 357 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{F}_2\text{NO}_2$ : 357.014 ( $\text{M}^+$ ), Found: 357.014; IR (KBr)  $\text{cm}^{-1}$ : 2977, 1246, 1123, 1091.

#### 4,4-Difluoro-5-methoxy-3-methyl-5-phenyl-4,5-dihydroisoxazole (4bD)

Colorless oil;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 2.16 (3H, d,  $J = 2.4$  Hz), 3.28 (3H, s), 7.44–7.47 (3H, m), 7.55–7.59 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.78, 51.49, 104.0 (dd,  $J = 33.2, 16.9$  Hz), 124.6 (dd,  $J = 269.4, 251.5$  Hz), 127.6, 128.6, 130.1, 130.4, 154.6 (dd,  $J = 29.2, 25.2$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -40.3 (1F, dq,  $J = 266.4, 2.4$  Hz), -68.0 (1F, d,  $J = 266.4$  Hz); MS  $m/z$ : 227 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{11}\text{H}_{11}\text{F}_2\text{NO}_2$ : 227.076 ( $\text{M}^+$ ), Found: 227.075; IR (neat)  $\text{cm}^{-1}$ : 3065, 2946, 1243, 1119.

#### 5'-((4,4-Difluoro-3,5-diphenyl-4,5-dihydroisoxazol-5-yl)-[1,1':3',1''-terphenyl]-2'-ol (6aK)

Colorless solid; M.p. 65.5–71.0 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.50 (1H, s), 7.31–7.54 (18H, m), 7.60–7.62 (2H, m), 7.86–7.88 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 90.51 (t,  $J = 23.3$  Hz), 128.2 (t,  $J = 260.2$  Hz), 125.2 (m), 126.8, 127.2, 127.7 (m), 127.9, 128.4, 128.6, 128.6, 128.9, 128.9, 129.0, 129.4, 131.2, 135.7 (m), 137.1, 149.6, 153.6 (t,  $J = 25.9$  Hz);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$ : -34.7 (1F, d,  $J = 257.8$  Hz), -35.5 (1F, d,  $J = 257.8$  Hz); MS  $m/z$ : 503 ( $\text{M}^+$ ); HRMS Calcd for  $\text{C}_{33}\text{H}_{23}\text{F}_2\text{NO}_2$ : 503.170 ( $\text{M}^+$ ), Found: 503.170; IR (KBr)  $\text{cm}^{-1}$ : 3533, 3060, 1496, 1469, 1233, 1106.

## Conflicts of interest

There are no conflicts to declare.

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